REMARKS

Prior to this amendment, claims 1, 19, 23-33, 35-39, 48, 49, and 52-54 are pending and Finally rejected, and claims 35, 36, 38, and 39 are withdrawn from consideration. By this Amendment, claims 1 and 25 are amended, claims 56-60 are added, and claims 19, 35, 36, 38, 39, and 49 are canceled.

Support for the amendment of claim 1 can be found throughout the specification, for example at page 14, lines 19-28; page 20, lines 17-30. Support for the amendment of claim 25 can be found in the specification at page 17, lines 13-17. Support for new claims 56-59 can be found in the specification at page 14, lines 19-28. Support for new claim 60 can be found in the specification at page 6, line 37.

No new matter has been added by this amendment. After entry of this amendment, **claims 1, 23-33, 37, 48, 52-54, and 56-60 are pending**. Unless specifically stated otherwise, none of these amendments are intended to limit the scope of any claim.

Withdrawal of Objections and Rejections:

Applicants thank Examiner Zeman for withdrawing the objections to the specification and claim 14 and 16, and the rejections of claims 1, 33, and 37

Examiner Interview:

Applicants thank Examiner Zeman for the courtesy of the telephone interview with their representatives Dr. Tanya Harding and Dr. Anne Carlson on July 8, 2004. During the interview, the rejection of the claims under 35 U.S.C. §112 were discussed extensively, as were the rejections under §103. Proposed amendments to the claims were reviewed during the interview, and Examiner Zeman indicated his willingness to consider such amendments and arguments as were discussed, in a filing that accompanied an RCE. Though agreement as to all matters was not reached, it is believed that this Amendment is in accordance with the interview.

Claim Rejection Under 35 U.S.C. §112, first paragraph:

Claims 1, 19, 23-33, 48-49, and 52-54 are rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification so as to enable one skilled in the art to which it pertains, or to which it is most nearly connected, to make and/or use the invention. Claims 19 and 49 have been canceled, rendering the rejection of these claims moot.

Regarding claims 1, 23-33, 48, and 52-54, Applicants respectfully traverse this rejection. MPEP §2402 states that a deposit may be required if "words alone cannot sufficiently describe how to make and use the invention." Furthermore, 37 C.F.R. §1.802(b) states that "[b]iological material need not be deposited, *inter alia*, if it is known and readily available to the public or can be made or isolated without undue experimentation."

The amino acid and nucleic acid sequences of SCFv(17b) are provided in SEQ ID NOs: 3 and 4, respectively. The provided amino acid and nucleic acid sequences of SCFv(17b) clearly enable the invention, and the specification provides additional support for making and using it. Thus, SCFv(17b) is clearly enabled by the specification and the sequence listing, and a deposit is not required.

Solely in the interest of advancing prosecution of this application, Applicants have amended claim 1 to recite wherein "the second binding domain is scFv(17b) and wherein the second binding domain is encoded by an amino acid sequence comprising at least 90% sequence identity to residues 244 through 502 of SEQ ID NO: 3." Residues 244 through 502 of SEQ ID NO: 3 correspond to the sequence of scFv(17b). Applicants believe that the amendment of claim 1 to include the combination of sequence identity ("at least 90% sequence identity") and functional language ("a second binding domain which forms a neutralizing complex") is sufficient to enable one of skill in the art to make and use the invention.

Claims 23-33, 48, and 52-54 depend, directly or indirectly, from claim 1 and incorporate all of the limitations therefrom. Applicants respectfully request that this rejection of claims 1, 23-33, 48, and 52-54 be withdrawn.

Claim Rejections Under 35 U.S.C. §103:

Traunecker et al. *in view of Sullivan* et al.

Claims 1, 19, 23-33, 48-49, and 52-55 are rejected as allegedly rendered obvious by Traunecker *et al.* (*International Journal of Cancer*, Supplement 7, 51-52, 1992) in light of Sullivan *et al.* (*Journal of Virology*, 72(6):4694-4703, 1998). Applicants traverse this rejection, as these documents, even in combination, do not teach or fairly suggest all of the elements of the claimed invention. Claims 19 and 49 have been canceled, rendering the rejection of those claims moot.

Applicants claim a fusion protein effective for neutralizing viral infection by binding to two sites on a single target gp120 envelope protein molecule. Without a linker capable of permitting the two domains of the fusion protein to bind to the same target gp120 envelope protein, the fusion protein is not capable of neutralizing the viral infection. At least this element of Applicants' invention is not taught by the cited references.

The Examiner states that Traunecker *et al.* discloses that the two binding domains are joined by a polypeptide linker (see the Office action at page 12). However, Applicants note that the linker disclosed in Traunecker *et al.* (see Figure 1B) joins together the heavy and light chains of the antibody portion of the molecule, and not the two different binding domains of the fusion protein. Applicants further note that the reference does not teach any benefits to including a linker sequence in the fusion; nor does it appear that Traunecker *et al.* contemplated the use of a linker to join the two binding domains.

Despite this, the Examiner states that one of skill in the art would have a high expectation of success since Traunecker *et al.* disclose that their "approach to design single chain molecules can be applied more generally" and the Examiner alleges that "the use of linkers is well known in the art and, in the absence of evidence to the contrary, the use [of] linkers with the sequence of either SEQ ID NO: 1 or SEQ ID NO: 2 would be obvious to one of skill in the art" (see the Office action at page 13).

However, Applicants believe that incorporating a linker in the fusion protein, and that the linker can and should be variable as taught in Applicants' specification, provides unexpectedly superior properties to the current invention. These properties would not have been obvious to someone reading the cited references. As taught in great detail throughout Applicants' specification (see, for instance, page 3, lines 28-36; page 11, line 33 through page 12, line 23; page 16, lines 30-34; page 17, line 31 through page 18, line 2; page 24, lines 4-8; and page 29, lines 1-12), the linker in the chimeric fusion protein is designed to be sufficiently long and flexible to allow the fusion protein to bind two sites at different regions of a single target molecule. Applicants' specification also teaches ways to test the effectiveness of a proposed linker, and to vary the length of the linker to optimize it for specific fusion protein/target systems (see, for instance, page 12, lines 17-23; page 16, lines 30-33; page 17, line 31 through page 18, line 2; the section beginning at page 24 – **Activity of Fusion Proteins**; and page 29, lines 8-12).

The inventors have published data since the filing of the subject application demonstrating that, surprisingly, not all HIV isolates are prevented from infecting $CD4^+$ cells in the presence of the chimeric fusion protein sCD4-scFv17b. This data is published in Dey *et al.* (*J. Virol.* 77:2859-2865, 2003, a copy of which is submitted herewith in an Information Disclosure Statement (IDS)). Dey *et al.* states that, despite guidance in the design of the chimeric protein from X-ray crystallographic data, it is possible that the distance between the two gp120 target sites are greater in resistant HIV strains than in the strain used to generate the crystallographic data (see page 2864, left column). This illustrates that the fusion protein must contain an effective linker peptide between the binding domains. It was necessary for Applicants to teach the benefits of varying the length and conformation of the linker, in order to enable the use of fusion proteins of the invention. Traunecker *et al.* does not teach use of a linker between the binding domains of the Janusin molecule, nor does that reference teach how to vary such a linker or test the functionality of the resultant fusion. Thus, Traunecker *et al.* does not teach the elements of Applicants' claims.

Applicants further remind the Examiner that Traunecker *et al.* does not teach any bispecific fusion construct that binds two sites on a single molecule.

Sullivan *et al.* teaches the induction of a 17b epitope by sCD4, as well as the virus-neutralizing abilities of the 17b and CG10 antibodies. Sullivan *et al.* does not disclose any type of bispecific fusion proteins, or peptide linkers. Thus, Sullivan *et al.* does not overcome the deficiency of Traunecker *et al.*, and the combination of these two references does not provide all of the limitations of the pending claims. Nor is there any indication in either reference that its teaching can or should be combined with the other; any combination of these two reference appears to be based on impermissible hindsight based on Applicants' teachings in the current application.

The cited references, alone or in combination, do not teach *functional* bispecific fusion proteins, containing a peptide linker, capable of binding two different domains on the same target molecule. Thus, Traunecker *et al.* and Sullivan *et al.* do not render obvious Applicants *functional* bispecific fusion protein, with a linker, where both domains bind to the same target molecule and neutralize HIV infection. In light of these arguments, Applicants respectfully request that this rejection be withdrawn.

Traunecker et al. *in view of Thali* et al.

Claims 1, 11-12, 14-19, 23-34, 37, 48-49, and 52-55 are rejected as allegedly rendered obvious by Traunecker *et al.* in light of Thali *et al.* (*Journal of Virology*, 67(7):3978-3988, 1993). Applicants note that claims 11, 12, 14-18, and 34 were previously canceled and will respond to the rejection as to claims 1, 23-33, 48, and 52-55. As discussed above, claims 19 and 49 have been canceled, rendering the rejection of these claims moot.

Applicants traverse this rejection, as the cited documents (Traunecker *et al.* and Thali *et al.*), even in combination, do not teach or fairly suggest all of the elements of the claimed invention.

As described above, Traunecker *et al.* does not teach a bispecific fusion molecule having a peptide linker and capable of binding two different sites on a target molecule, which molecule can effectively neutralize HIV infection. Nothing in Traunecker *et al.* would have taught one of

ordinary skill in the art to generate a functional bispecific fusion protein comprising two domains connected by a peptide linker, where both domains bind to the same target molecule and thereby neutralize HIV infection.

Thali *et al.* teaches that the 17b and 48d antibodies bind gp120 and neutralize a variety of HIV-isolates. In addition, Thali *et al.* discloses that recognition of the 17b and 48d epitopes by these antibodies is dependent upon the conformation of gp120. However, Thali *et al.* does not disclose any type of bispecific fusion proteins or peptide linkers. Thus, Thali *et al.* does not overcome the deficiency of Traunecker *et al.* and the combination of these references does not provide all of the limitations of the pending claims. Nor is there any indication in either reference that its teaching can or should be combined with the other; any combination of these two reference appears to be based on impermissible hindsight based on Applicants' teachings in the current application.

In light of these arguments, Applicants respectfully request that this rejection be withdrawn.

Secondary Considerations

Applicants believe the Office has not demonstrated a *prima facie* case of obviousness in either of the rejections discussed above. Even if it were assumed that the invention is *prima facie* obvious, secondary considerations, such as recognition of the invention by those skilled in the art, illustrates that it is non-obvious.

Various publications refer to the bispecific fusion protein described in Dey *et al.* and in the subject application, and comment on the novelty and effectiveness of the fusion. For instance, in Vermeire & Schols (*J. Leuk. Biol.*, 74:667-675, 2003, a copy of which is submitted herewith in the IDS), the authors comment on the invention as follows:

> "Recently, a novel sCD4-based HIV-1 neutralizing agent has been reported (reference 37 [Dey *et al.*, 2003]). This agent, designated sCD4-17b, is a recombinant chimeric protein containing sCD4 attached via a flexible polypeptide linker to a human mAb that targets a conserved CD4-induced epitope on gp120 overlapping the coreceptor-

> binding region. sCD4-17b can bind to gp120 simultaneously via two independent moieties (*i.e.*, the CD4 binding site and the masked coreceptor binding site which is exposed only after a CD4-induced conformational change) and showed higher neutralizing activity against HIV-1 as compared with the neutralizing mAbs IgG1 b12, IgG1 2G12, and IgG3 2F5." (*right hand column, page 668*)

In addition, the authors in Liao *et al.* (*J. Virol.*, 78:5270-5278, 2004, a copy of which is submitted herewith in the IDS) praise the inventors' fusion construct as "potent," notably in contrast to their own work:

> While A32-rgp120 complexes with rgp12089.6 induced slightly more neutralizing breadth than rgp12089.6 alone, comparative studies with A32-rgp120BaL showed that A32-rgp120BaL complexes were less immunogenic for broadly reactive NA than uncomplexed rgp120BaL (Tables 2 and 5). Thus, our carefully characterized A32-rgp120 complexes provide the first data demonstrating that exposure of the coreceptor binding site alone is not sufficient for induction of broadly reactive NA. Immunofluorescence studies on live HIV-infected cells have shown limited accessibility of the coreceptor binding site during fusion (8). In contrast, the fusion protein CD4-17b Fab is a potent bivalent inhibitor of most HIV-1 primary isolates (reference 7 [Dey *et al.*, 2003]). Clearly envelope constructs more native than A32-rgp120 monomers, such as A32-bound gp140 or gp160 trimers, need to be tested as immunogens. (*right hand column, page 5276*)

Yet other authors have specifically acknowledged the inventors' fusion protein as "novel," as illustrated in the review by Roehr (*amfAR* 3(4):1-8, Aug/Sept. 2002, a copy of which is submitted herewith in the IDS):

> Determining the crystal structure of gp120 and the process of the conformational changes that HIV undergoes during the process of binding with cell coreceptors has allowed development of a novel neutralizing agent, sCD4-17b. (*left hand column, page 3*)

The inventors are also aware of other researchers that are making analogous constructs using different antibodies. Taken together, all of these accolades by those skilled in the art – reviewer comments, published commentary, and copying of the method of the invention -- further attests to the non-obviousness and interest of the Applicants' approach.

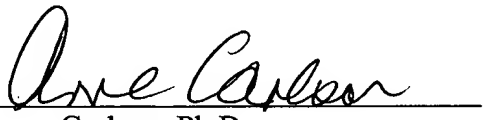
In light of these arguments, Applicants respectfully request that the rejection of claims 1, 23-33, 48, and 52-55 under 35 U.S.C. §103 be withdrawn.

CONCLUSIONS

Based on the foregoing amendments and arguments, the claims are in condition for allowance and notification to this effect is requested. If for any reason the Examiner believes that a telephone conference would expedite allowance of these claims, please telephone the undersigned at (503) 226-7391.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By 

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